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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,056	GRAINGER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153,154,157-165 and 169-182* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153,154,157-165 and 169-182* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/4/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 12/4/2008 amending claims 153, 154, 169, 174, 175 and adding new claims 177-182. Claims 1-152, 155-156, 166-168 have been canceled. Claims 153-154, 157-165, 169-182 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' amendment of claims regarding structural analog of tamoxifen, stilbene antisteroid, a 1, 2 diphenylethane antisteroid, or a naphthalene antisteroid comply with the priority date of 6/7/1995 as claimed. The rejection of claims 153, 154, 157-165, 169-176 under 35 U.S.C. 112, first paragraph written description and rejection of claims 153-155, 157-168 under 35 U.S.C. 112, first paragraph enablement, the rejection of claims 153, 154, 160, 158, 165, 169, 170, 174, 175 under 35 U.S.C. 102(b) as being anticipated by Connolly et al. (U.S.Patent No. 5,250,561) is withdrawn due to the amendment of claims. The double patenting rejection is maintained and are given below for Applicants' convenience. Applicants' arguments regarding the 103 rejections have been fully considered but they are moot in view of new rejections presented in this action. Applicants' amendments necessitated the new rejections presented in this office action. Accordingly, the action is made Final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226

(Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 153, 154, 157-165, 169-175, 181, 182 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194,196-203, 205-211 and 231 of copending Application No. 09/754,775. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the method claimed in claims 153, 154, 157-165, 169-175 of the instant application utilizes the same biological pathway comprising increasing the level of TGF-beta encompassing utilizes the same active agents in the method of claim 173 of the co-pending application. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153-154, 157-165, 169-182 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not teach administration of any of the claimed compounds in treating cardiovascular indication in mammals and the compounds claimed in treating cardiovascular indication have different biological activities, bioavailabilities, pharmacokinetic profiles, and pharmacological efficacy and does not reasonably provide enablement for a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen and is a structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof.

(2) Breadth of the Claims:

The instant claims are broad and embrace treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen and is a structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof. The claims are broad with respect to the different agents claimed because there are a

number of structural analogs of tamoxifen, stilbene antisteroids, 1, 2 diphenylethane antisteroids and naphthalene antisteroids known and yet to be discovered.

(3)/(4) Guidance of the Specification and Working Examples

The specification provides guidance and working examples related to: 1) impact of Tamoxifen on Vascular Smooth Muscle Cells and the Relationship thereof to TGF-Beta Production and Activation Cell culture, DNA synthesis assay and cell counting (2) heparin Effect on VSMC Proliferation and Differentiation (3) comparison of Enzyme-Dispersed and Explant-Derived Human VSMC (4) TGF-beta and Transgenic apo(a) Mice - used to study whether inhibition of TGF-beta activation, resulting in enhanced VSMC proliferation, represents a key step in atherogenesis (5) Tamoxifen Inhibits Migration and Lipid Uptake in VSMC in vitro and in Transgenic Mice (6) Effect of Idoxifene on Cultured Human VSMCs (7) Tamoxifen elevates TGF-.beta. and suppresses diet-induced formation of lipid lesions in mouse aortae (8) Determination of Active and Acid Activatable TGF-.beta. in Human Sera, Platelets and Plasma by Enzyme-Linked Immunosorbent Assays (9) Association of TGF-beta with Lipoprotein Particles. However, there are no working examples and the specification does not teach administration of claimed agent(s) to a mammal in general or to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

(5) State/Predictability of the Art:

There is prior art teachings regarding lowering serum level cholesterol levels thereby treating or improving atherosclerotic conditions comprising administering to patients raloxifene (Black et al. U.S. 5,464,845), droloxifene (Fontana U.S. 5,426,123). The method of treating lipid accumulation, increase plaque stability comprising administering agents that include tamoxifen, tamoxifen analogs is predictable from the prior art. However, it is not predictable from the prior art that all known and yet to discover compounds of class, stibene antisteroids, naphthalene antisteroids etc will be useful in a method of treating a cardiovascular indication characterized by a decreased lumen diameter as there are teachings that relate to the side effects or toxic effects of drugs like hexesterol, clomiphene. Biofarma document (www.biofarma.kiev.ua\) teaches hexesterol's side effects include nausea, vomiting, vertigo and an administration of large/high doses cause toxic liver injury, excessive endometrium proliferation etc and the contraindications include diseases of the liver and kidney, malignant and benignant neoplasms in women under to , diseases connected with heightened level of blood coagulation etc and there are drug interactions involved with other medicinal products such as progesterone, pregnin etc. The document regarding clomiphene (drugs.com, clomiphene citrate) teaches that patients with liver disease, have undiagnosed vaginal bleeding, endometriosis, ovarian cysts etc should not take clomiphene and further teach that the side effects include allergy reactions, ovarian hyperstimulation syndrome etc.

(6) The Quantity of Experimentation Necessary:

In order to enable the instantly claimed methods that commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct experiments testing the compounds claimed for treating a cardiovascular indication. In order to practice the above claimed invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system to test the composition in a method of treatment of cardiovascular indication. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Considering the side effects, drug interactions and contraindications of compounds like clomiphene, hexesterol in the prior art this would be an arduous and daunting task. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a cardiovascular indication administering TGF-beta agent that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen and is a structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid in a mammal.. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in

return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 153, 154, 157-158, 160-163, 165, 169, 170-173, 181-182 are rejected under 35 U.S.C. 102(e) as being anticipated by Black et al. (U.S. 5,464,845, filing date Nov 30 1993).

Black et al. teaches a method of lowering serum cholesterol levels comprising administering to a patient a serum cholesterol lowering amount of a compound such as raloxifene (see abstract, claims 1, 7-9). Applicants' in the specification teach raloxifene as a structural analog of tamoxifen (para 0046). Black et al. reference also teaches that raloxifene was substantially less estrogenic than tamoxifen (col. 22, lines 19-21). Also,

the reference teaches that when cholesterol accumulates in the wrong place, for example within the wall of an artery, it cannot be readily mobilized and its presence leads to the development of an atherosclerotic plaque. Elevated concentrations of serum cholesterol associated with low density lipoproteins have been demonstrated to be a major contributing factor in the development and progression of atherosclerosis. The reference further teaches that in mammals, serum lipoprotein is composed of cholesterol together with cholesteryl esters, triglycerides, phospholipids and apoproteins and abundant evidence indicates that treatment of hyperlipoproteinemia may diminish or prevent atherosclerotic complications (col. 1, lines 23-31, 63-65). Black teaches that the particular dosage of a compound of formula I such as raloxifene required to lower serum cholesterol levels will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician and generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg (col. 8, lines 39-42). Applicants' in the specification (para 0118) teach that for TGF-beta activators or production stimulators, such as compounds of the formula (I), several exemplary dosing regimens are contemplated, depending upon the condition being treated and the stage to which the condition has progressed and for prophylactic purposes with respect to atherosclerosis, for example, a low chronic dose sufficient to elevate in vivo TGF-beta production is contemplated and an exemplary dose of this type is about 0.1 mg/kg/day (ranging between about 0.1 and about 10 mg/kg/day), preferably about 0.1-1.0 mg/kg/day, most preferably about 0.3 mg/kg/day. Thus a patient of 70 kg body weight would require a cytostatic dose ranging from 7-70 mg/kg/day. Thus, Black

et al. teach the dosage amount that is claimed in the instant application. The reference teaches administration of the compounds including raloxifene by various modes including oral, intramuscular, intravenous and transdermal and are well suited to formulation as sustained release dosage forms and the like. (col. 5, lines 30-36). It is inherent property of the agent, raloxifene to increase the level of TGF-beta, or act as a stimulator or an activator and to increase the production of TGF-beta mRNA. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties of the compound Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed product. Black et al. anticipates the teaching of a method of treating a vascular indication in a mammal selecting an agent such as raloxifene, a structural analog of tamoxifen comprising administering a cytostatic dose of the agent to the mammal with decreased lumen as a result of atherosclerosis in an amount effective to inhibit lipid accumulation.

Claims 153, 154, 157-158, 160-163, 165, 169, 170-173, 181-182 are rejected under 35 U.S.C. 102(e) as being anticipated by Fontana (U.S. 5,426,123, filing date May 11 1994).

Fontana teaches a method of lowering serum cholesterol levels, comprising administering to a human in need of treatment an effective amount of a compound of

formula (I) including compound droloxifene as a preferred one (col. 2, lines 58-62, claims 1-3, see abstract). Applicants' in the specification teach droloxifene as a stilbene-type antisteroid (para 0046). Fontana in the introduction teaches that all mammalian cells require cholesterol as a structural component of their cell membranes and for non-sterol end products and when cholesterol accumulates in the wrong place, for example within the wall of an artery, it cannot be readily mobilized and its presence leads to the development of an atherosclerotic plaque, elevated concentrations of serum cholesterol associated with low density lipoproteins (LDL'S) have been demonstrated to be a major contributing factor in the development and progression of atherosclerosis. The reference further teach that compounds of formula I such as droloxifene provide an effective and acceptable treatment for hyperlipidemia/ hypercholesterolemia (col. 1, lines 10-40, 59-61). The reference further teaches that a typical daily dose will contain a nontoxic dosage level of from about 0.25 mg to about 400 mg/day of a compound of the present invention and preferred daily doses generally will be from about 1 mg to about 20 mg/day. Applicants' in the specification (para 0118) teach that for TGF-beta activators or production stimulators, such as compounds of the formula (I), several exemplary dosing regimens are contemplated, depending upon the condition being treated and the stage to which the condition has progressed and for prophylactic purposes with respect to atherosclerosis, for example, a low chronic dose sufficient to elevate in vivo TGF-beta production is contemplated and an exemplary dose of this type is about 0.1 mg/kg/day (ranging between about 0.1 and about 10 mg/kg/day), preferably about 0.1-1.0 mg/kg/day, most preferably about 0.3 mg/kg/day. Thus a patient of 70 kg

body weight would require a cytostatic dose ranging from 7-70 mg/kg/day. Thus Fontana teach the dosage amount that is claimed in the instant application. Also, the reference teaches that the compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subucutaneus, intravenous, intramuscular, and intranasal and these compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician (col. 4, lines 55-60). The reference teaches that the compounds including droloxifene are well suited to formulation as sustained release dosage forms and the like (col. 5, lines 28-30). It is inherent property of the agent, raloxifene to increase the level of TGF-beta, or act as a stimulator or an activator and to increase the production of TGF-beta mRNA. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties of the compound Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed product. Fontana anticipates the teaching of a method of treating a vascular indication in a mammal selecting an agent such as droloxifene, a stilbene-type antisteroid comprising administering a cytostatic dose of the agent to the mammal with decreased lumen as a result of atherosclerosis in an amount effective to inhibit lipid accumulation.

Claims 153, 154, 157-158, 160-163, 165, 169, 170-177, 181-182 are rejected under 35 U.S.C. 102(e) as being anticipated by Sall (U.S. 5,441,965, filing date Dec 21 1993).

Sall et al. teaches a method of inhibiting thrombin and its attending diseases and conditions comprising administering to a human in need of treatment an effective amount of a compound including raloxifene (see Abstract, claims 1-3). Accordingly, the reference teaches a method of treating thrombosis comprising administering a tamoxifen structural analog such as raloxifene. The reference teaches that the compound such as raloxifene is useful as an anticoagulant for prophylaxis and treatment of thromboembolic diseases such as venous thrombosis, pulmonary embolism, arterial thrombosis, in particular myocardial ischemia, myocardial infarction and cerebral thrombosis, general hypercoagulable states and local hypercoagulable states, such as following angioplasty and coronary bypass operations, and generalized tissue injury as it relates to the inflammatory process. Hence the reference teaches that raloxifene can be administered to patients subjected to vascular procedures. It is inherent that upon administration of the same agent as claimed will inhibit the smooth muscle proliferation associated with the procedural vascular trauma (col. 2, lines 1-15). The reference teaches that the particular dosage of a compound of formula I required to inhibit thrombin in the appropriate diseases and conditions, according to this invention will depend upon the severity and nature of the condition, the route of administration, and related factors that will be decided by the attending physician and generally accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and

more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively inhibit thrombin or its attending diseases or conditions (col. 4, lines 1-14). Applicants' in the specification (para 0118) teach that for TGF-beta activators or production stimulators, such as compounds of the formula (I), several exemplary dosing regimens are contemplated, depending upon the condition being treated and the stage to which the condition has progressed and for prophylactic purposes with respect to atherosclerosis, for example, a low chronic dose sufficient to elevate in vivo TGF-beta production is contemplated and an exemplary dose of this type is about 0.1 mg/kg/day (ranging between about 0.1 and about 10 mg/kg/day), preferably about 0.1-1.0 mg/kg/day, most preferably about 0.3 mg/kg/day. Thus a patient of 70 kg body weight would require a cytostatic dose ranging from 7-70 mg/kg/day. Thus, Sall et al. teach the claimed dosage of the agent such as raloxifene in a method of treating a cardiovascular indication. The reference teaches that the drug such as raloxifene is administered orally, intramuscularly, intravenously and transdermally and further teach that the drugs may be formulated as sustained release dosage forms and the like (col. 2, lines 33-37). It is inherent property of the agent, raloxifene to increase the level of TGF-beta, or act as a stimulator or an activator and to increase the production of TGF-beta mRNA. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties of the compound Applicant discloses and/or claims

are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed product. Sall et al. teachings anticipates a method of treating a vascular indication in a mammal selecting an agent such as droloxifene, a stilbene-type antisteroid comprising administering a cytostatic dose of the agent to the mammal with decreased lumen as a result of thrombosis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 153, 154, 157-158, 160-163, 165, 169, 170-176, 178, 181-182 are rejected under 35 U.S.C. 102(a) as being anticipated by Fontana (U.S. 5,384,332).

Fontana teaches a method for inhibiting aortal smooth muscle cell proliferation comprising administering to a human in need of treatment an effective amount of a compound of formula I such as droloxifene (See abstract, claims 1-3). The reference teaches that “Aortal smooth muscle cell proliferation plays an important role in diseases such as atherosclerosis and restenosis. Vascular restenosis after percutaneous transluminal coronary angioplasty (PTCA) has been shown to be a tissue response characterized by an early phase is due to thrombosis with some vasospasms while the late phase appears to be dominated by excessive proliferation and migration of smooth

muscle cells". The reference further teaches that vascular restenosis remains a major long term complication following surgical intervention of blocked arteries by percutaneous transluminal coronary angioplasty (PTCA), atherectomy, laser angioplasty, and arterial bypass graft surgery and agents that inhibit the proliferation and/or migration of aortal smooth muscle cells are useful in the treatment and prevention of restenosis and the teachings provides for the use of compounds of formula I including droloxifene as aortal smooth muscle cell proliferation inhibitors (see Background of the invention). The reference teaches a nontoxic dosage level of about o.25 mg to 400 mg/day of the drug and by a variety of routes including oral, rectal, transdermal, subucutaneus, intravenous, intramuscular, and intranasal. Additionally, the reference teaches that the drugs are well suited to formulation as sustained release dosage forms and the like (col. 5, lines 20-30, col. 6, lines 1-2). Applicants' in the specification (para 0118) teach that for TGF-beta activators or production stimulators, such as compounds of the formula (I), several exemplary dosing regimens are contemplated, depending upon the condition being treated and the stage to which the condition has progressed and for prophylactic purposes with respect to atherosclerosis, for example, a low chronic dose sufficient to elevate in vivo TGF-beta production is contemplated and an exemplary dose of this type is about 0.1 mg/kg/day (ranging between about 0.1 and about 10 mg/kg/day), preferably about 0.1-1.0 mg/kg/day, most preferably about 0.3 mg/kg/day. Thus a patient of 70 kg body weight would require a cytostatic dose ranging from 7-70 mg/kg/day. Thus Fontana teach the dosage amount that is claimed in the instant application. It is inherent property of the agent, raloxifene to

increase the level of TGF-beta, or act as a stimulator or an activator and to increase the production of TGF-beta mRNA. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties of the compound Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed product. Fontana anticipates the teaching of a method of treating a vascular indication in a mammal selecting an agent such as droloxifene, a stilbene-type antisteroid comprising administering a cytostatic dose of the agent to the mammal with decreased lumen in a method of inhibiting smooth muscle cell proliferation that plays an important role in diseases such as atherosclerosis and restenosis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 159 is rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al. (U.S. 5,464,845, filing date Nov 30 1993).

Black et al. teachings discussed as above. The reference teaches that the compounds including raloxifene is well suited to formulation as sustained release dosage forms.

The reference does not teach the agent administered is in sustained release dosage form for treating vascular indication.

The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Thus it would have been obvious to one of obvious to administer a sustained release dosage drug of an agent such as raloxifene in treating cardiovascular indication. One having ordinary skill in the art at the time of the invent ion would have been motivated in administering a sustained release dosage form for treating vascular indication is to obtain desirable therapeutic benefits in a continuous, controlled slow release of the drug.

Claim 159 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fontana (U.S. 5,426,123).

Fontana's teachings discussed as above. The reference teaches that the compounds including droloxifene is well suited to formulation as sustained release dosage forms.

The reference does not teach the agent administered is in sustained release dosage form for treating vascular indication.

The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Thus it would have been obvious to one of obvious to administer a sustained release dosage drug of an agent such as raloxifene in treating cardiovascular indication. One having ordinary skill in the art at the time of the invent ion would have been motivated in administering a sustained release dosage form for treating vascular indication is to obtain desirable therapeutic benefits in a continuous, controlled slow release of the drug.

Claim 159 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fontana (U.S. 5,384,332).

Fontana's teachings discussed as above. The reference teaches that the compounds including droloxifene is well suited to formulation as sustained release dosage forms.

The reference does not teach the agent administered is in sustained release dosage form for treating vascular indication.

The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Thus it would have been obvious to one of obvious to administer a sustained release dosage drug of an agent such as raloxifene in treating cardiovascular indication. One having ordinary skill in the art at the time of the invent ion would have been motivated in administering a sustained release dosage form for treating vascular indication is to obtain desirable therapeutic benefits in a continuous, controlled slow release of the drug.

Claim 159 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sall (U.S. 5,441,975, filing date Dec 21 1993).

Sall et al. teachings discussed as above. The reference teaches that the compounds including raloxifene is well suited to formulation as sustained release dosage forms.

The reference does not teach the agent administered is in sustained release dosage form for treating vascular indication.

The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Thus it would have been obvious to one of obvious to administer a sustained release dosage drug of an agent such as raloxifene in treating cardiovascular indication. One having ordinary skill in the art at the time of the invent ion

would have been motivated in administering a sustained release dosage form for treating vascular indication is to obtain desirable therapeutic benefits in a continuous, controlled slow release of the drug.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al. (U.S. 5,464,845, filing date Nov 30 1993) in view of Cullinan et al. (U.S. 5,457,113).

Black et al. teachings discussed as above.

The reference does not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent in treating cardiovascular indication because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit lipid accumulation is to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fontana (U.S. 5,426,123) in view of Cullinan et al. (U.S. 5,457,113).

Fontana's teachings discussed as above.

The reference does not teach the administration of the agent via stent.

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It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent in treating cardiovascular indication because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit lipid accumulation is to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fontana (U.S. 5,384,332) in view of Cullinan et al. (U.S. 5,457,113).

Fontana's teachings discussed as above.

The reference does not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent in treating cardiovascular indication because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit lipid accumulation is to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sall (U.S. 5,441,975, filing date Dec 21 1993).

Sall et al. teachings discussed as above.

The reference does not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent in treating cardiovascular indication because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit lipid accumulation is to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claims 174-177 are rejected as being unpatentable over Black et al. (U.S. 5,464,845, filing date Nov 30 1993) in view of Sall (U.S. 5,441,975, filing date Dec 21 1993).

Black et al. teachings discussed as above.

The reference does not teach that the patient is subjected to procedural vascular trauma.

Sall et al. teachings discussed as above. The reference teaches that the drug such as raloxifene useful in treating thrombosis can be administered following angioplasty and coronary bypass operations, and generalized tissue injury as it relates

to the inflammatory process. Hence the reference teaches that raloxifene can be administered to patients subjected to vascular procedures.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent such as raloxifene in treating a cardiovascular indication to patients subjected to procedural vascular trauma because of the teachings of Sall et al. One having ordinary skill in the art would have been motivated in administering an agent such as raloxifene to patients subjected to procedural vascular trauma in expectation of success and to obtain desirable therapeutic effects such as treating thrombosis in such patients.

Claims 179 and 180 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fontana (U.S. 5,384,332) in view of Willson (U.S 5.681.835, effective filing date, Apr 25 1994).

Fontana's teachings discussed as above.

The reference does not teach the drug for treating cardiovascular indication to be 1, 2 diphenylethane antisteroid or a naphthalene antisteroid like nafoxidene.

Willson teaches hexestrol, raloxifene, droloxifene, nafoxidene as non-steroidal anti-estrogen compounds (col. 2, lines 20-22).

It would have been obvious to one of ordinary skill in the art to use an antisteroid such as hexestrol in a method of treating a cardiovascular indication as claimed because Willson teaches the equivalence of compounds raloxifene, droloxifene and hexestrol. Fontana teaches the function of droloxifene as a smooth muscle proliferation inhibitor. One having ordinary skill in the art would have been motivated to substitute

one non-steroidal anti-estrogen compound (hexestrol or nafoxidene) for droloxifene in Fontana's studies in expectation of similar or better therapeutic benefits.

Claims 179 and 180 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sall (U.S. 5,441,975, filing date Dec 21 1993) in view of Willson (U.S 5.681.835, effective filing date, Apr 25 1994).

Sall's teachings discussed as above.

The reference does not teach the drug for treating cardiovascular indication to be 1, 2 diphenylethane antisteroid or a naphthalene antisteroid like nafoxidene.

Willson teaches hexestrol, raloxifene, droloxifene, nafoxidene as non-steroidal anti-estrogen compounds (col. 2, lines 20-22).

It would have been obvious to one of ordinary skill in the art to use an antisteroid such as hexestrol in a method of treating a cardiovascular indication as claimed because Willson teaches the equivalence of compounds raloxifene, droloxifene and hexestrol. Fontana teaches the function of droloxifene as a smooth muscle proliferation inhibitor. One having ordinary skill in the art would have been motivated to substitute one non-steroidal anti-estrogen compound (hexestrol or nafoxidene) for droloxifene in Fontana's studies in expectation of similar or better therapeutic benefits.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Applicants' amendments necessitated the new rejections presented in this office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617